



MISSOURI DEPARTMENT OF
HEALTH

Syntex - Verona
ID #: MOD 00745254
Break: 3.4
Other: 7-17-92

JDB

John Ashcroft
Governor

John R. Bagby, Ph.D.
Director

P.O. Box 570, Jefferson City, MO 65102 • 314-751-6400 • FAX 314-751-6010

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July 17, 1992

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SPFD BRANCH

Mr. Robert Morby
Chief
Superfund Branch
Waste Management Division
U. S. Environmental Protection Agency
726 Minnesota Ave.
Kansas City, KS 66101



40032239
SUPERFUND RECORDS

Dear Mr. Morby:

The Missouri Department of Health (DOH) has reviewed the risk assessment for the Syntex Facility near Verona, MO. In general, the document appears to follow current Environmental Protection Agency (EPA) guidance. For the most part, slope factors and reference doses used in the risk assessment are current. Exposure variables used to estimate chemical intake are generally reasonable. However, there are several issues which should be clarified or corrected within the document. A discussion of these issues is provided in an attachment to this letter.

Thank you for the opportunity to review this document. If you have any questions, please feel free to call Ms. Cherri Baysinger-Daniel at (314) 751-6102.

Sincerely,

Daryl W. Roberts
Chief
Bureau of Environmental Epidemiology

Attachments

DWR:CBD:de



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Comments on the Draft Risk Assessment for the Syntex-Verona Facility, Verona, MO

1. Page 2-1, section 2.1. The last two lines of this paragraph appear to belong in the risk characterization section.
3. Page 2-3, sections 2.6.1 and 2.6.2. Terms such as "good water quality" and "poorer water quality" have little meaning. The parameters which cause water in the deeper aquifer to be of "good quality" and water in the shallow aquifer to be of "poorer quality" should be described in the text.
4. Page 2-4, section 2.6.3, second paragraph. A minus sign (-) may have been omitted from the third sentence.
5. Page 2-4, section 2.6.3, second paragraph. It appears the sections reading "where V = average . . ." and "Using this relationship . . ." have been reversed.
6. Page 2-5, section 2.7.1, first paragraph. This section is somewhat confusing. Monitoring well 1 is not listed among the ten original wells, but monitoring well 2 is listed as both a background well and a well to investigate the spray irrigation area. Confusion in this case may result from typographical errors and the remaining text in the section is difficult to follow. The inclusion of a site map with all buildings, trenches, streams, monitoring wells, etc. indicated would make this section much easier to follow.
7. Page 2-6, section 2.7.1, second paragraph. It is not clear from the text if none of the trench wells were producing water, or if wells 17 and 18 were not producing water.
8. Page 2-7, section 2.8, third paragraph. Please explain the rationale behind combining all but the last sampling rounds to estimate historical contaminant concentrations. If the goal was to estimate future contaminant concentrations, it seems that all sampling rounds would have been combined and a future mean and 95th UCL calculated using the entire data set. To estimate current conditions, data from the most recent round or two could be extracted and used.
9. Tables 2-3, 2-4 and 2-5. It is not clear from either the text or these tables if individual data points from all wells during all sampling periods were combined to obtain the values presented in these tables or if data from each well was summarized, then data points from the various wells were summarized to obtain the values presented. Statistically, the second method presented above may be more appropriate. The method used to calculate these values should be clearly presented and justified in the text.
9. Page 2-7, section 2.8, third paragraph. Without an adequate description of the site or a site map, it is difficult for a reader to understand why the trench wells are not representative of the site. Please define the factors which were taken into account when making this decision.
10. Page 3-6, section 3.2.4. A generic equation is given for HIF in this section. Does the chemical concentration term belong in this equation? If the equation is correct as presented, this formula is equivalent to that for the equation given for calculation of the Daily Intake (page 3-4, section 3.4). Please revise/correct these equations.

11. Page 3-7, section 3.4.2. All exposure assumptions (variable values used to calculate intake) and specific equations used to calculate intakes should be presented, either in a table or in the text. Sources for each variable should also be presented (see comment 24).
12. Page 4-1, section 4.1.2. Should "Table 6-1" read "Table 4-1"?
13. Page 4-4, section 4.2.5. EPA currently recommends using the Lead Biokinetic Uptake model to assess exposure to lead instead of an MCL.
14. Page 4-10, section 4.2.10. EPA's Environmental Criteria and Assessment Office has provided a provisional chronic RfD of 6×10^{-3} mg/kg/day for TCE (copy of memo enclosed). Although this is not a verified value, it can be used in a risk assessment with appropriate explanation in the uncertainty section.
15. Page 5-1, section 5.1. The description of the area around the immediate vicinity of the facility does not seem to be accurate. The town of Verona is located directly east of the Syntex facility. There is a small predominantly commercial area within 500 feet of the facility border. Residences surround the commercial area on the north, east and south. While the area to the north, south and west of the site is predominantly rural, the area to the east is not.
16. Page 5-2, section 5.2.1.1. Please identify the chemicals contributing most to the risk in the text. This comment also applies to sections 5.2.1.2, 5.2.2.1 and 5.2.2.2.
17. Page 5-2, section 5.2.1.1. If the reason behind separating a 30-year exposure into child, adolescent and adult receptor periods was to get a more real-life estimate of risk, it seems the risks associated with these periods should be summed. If getting a more real-life risk estimate was not the rationale behind splitting out the three periods, the rationale should be explained in the text. This comment also applies to sections 5.2.1.2, 5.2.2.1 and 5.2.2.2.
18. Page 5-2, section 5.2.1.1, third paragraph. "Exposure" is misspelled on the last line of this paragraph.
19. Page 5-2, section 5.2.1.2. The title of this section [Risks Associated with Future (Historic) Conditions] seems somewhat oxymoronic.
20. Page 5-5, section 5.3.1. This paragraph reads as if two sets of risk calculations, one for average exposure scenarios and one for reasonable maximum exposures, have been done. Please indicate exactly where this is presented in the risk assessment or reword the paragraph for clarification.
21. Page 5-5, section 5.3. The discussion of uncertainty in the risk assessment is confusing. Please rework this section for clarity and readability.
22. Page 6-1, section 6.1. This section does not appear to belong with this risk assessment. Please revise it to fit the current document or delete it.
23. Page 6-1, section 6.2. Please define a "maximum UCL" or reword this sentence.
24. Appendix A. This material should be presented in the body of the risk assessment.

25. Page A-1, under Ingestion of Ground Water. Please indicate the location of the Vandale Junkyard site in relation the Syntex-Verona Facility.
25. Appendix B. Tables A-1 through A-3 list 350 days/year as the Exposure Frequency (EF). The worksheets presented in Appendix B list 338 days as the EF. Please indicate which value was actually used in risk calculations and revise all tables for consistency.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF RESEARCH AND DEVELOPMENT
ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
CINCINNATI, OHIO 45268

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APR 13 1992

REML SECTION

APR 10 1992

SUBJECT: Provisional oral RfD for trichloroethylene.
(CAS #79-01-6)

FROM: Joan S. Dollarhide *Joan S Dollarhide*
Associate Director
Superfund Health Risk Technical Support Center
Chemical Mixtures Assessment Branch

TO: Dave Crawford
U.S. EPA
Region VII

This memo contains our most recent assessment for a provisional oral RfD for trichloroethylene. Please note that the attached information has not been through the Agency's review process and therefore does not represent an Agency verified risk assessment.

If we can be of further assistance, please feel free to contact the Superfund Technical Support Center at FTS 684-7300.

Attachment

cc: J. Dinan (OS-230)
B. Means (OS-230)
K. Poirier (ECAO-Cin)
M. Williams (Region VII)



Attachment

Risk Assessment Issue Paper for: Provisional Oral RfD for Trichloroethylene (CAS # 79-01-6)

INTRODUCTION

An oral RfD is not available for trichloroethylene on IRIS (U.S. EPA, 1992a) or the HEAST (U.S. EPA, 1991a). The RfD/RfC status report (U.S. EPA, 1992b) states that the RfD is under review, but cites 7/22/85 as the last Work Group meeting concerning this RfD. OHEA documents listed on the CARA list (U.S. EPA, 1991c) include WQCDs (U.S. EPA, 1980), HADs (U.S. EPA, 1985; 1987a), and HEAs (U.S. EPA, 1984; 1988). None of these documents derived an oral RfD for trichloroethylene.

The Drinking Water list (U.S. EPA, 1991b) provides a value of $7\text{E}-3$ mg/kg/day for the oral RfD for trichloroethylene with an associated DWEL of 0.3 mg/l; these toxicity values were derived in an ODW Health Advisory on trichloroethylene (U.S. EPA, 1987b). The basis for the RfD was a free-standing LOAEL for elevated liver weights in rats exposed to inhaled trichloroethylene for 14 weeks (Kimmerle and Eben, 1973). The derivation involved a determination of an absorbed dose for humans using the rat LOAEL, human inhalation rates and body weights, an absorption efficiency ratio of 0.3, and adjustments for continuous exposure. The absorbed dose (7.35 mg/kg/day) was divided by an uncertainty factor of 1000 (10 for the use of a LOAEL, 10 for interspecies extrapolation, and 10 for intraspecies variation).

ATSDR has prepared two Toxicological Profiles on trichloroethylene (ATSDR, 1989; 1991). The 1989 document derived an intermediate oral MRL of $2.2 \text{ E}+0$ mg/kg/day based on a NOAEL (217 mg/kg/day) for renal effects (increased urinary ketone and protein levels) in mice exposed to trichloroethylene in drinking water for six months (Tucker et al., 1982). The 1991 document derived an intermediate oral MRL of $1\text{E}-1$ mg/kg/day based on a LOAEL of 100 mg/kg/day for increased liver weight in mice exposed by gavage for 4 weeks (Buben and O'Flaherty, 1985). Neither document derived a chronic oral MRL for trichloroethylene.

To identify research reports pertinent to the derivation of a chronic RfD for trichloroethylene, EPA and ATSDR documents on trichloroethylene (as cited above) and the HSDB, RTECS and TSCATS databases were reviewed; in addition, a computer search of the literature was conducted (TOXLINE, 1989 - January, 1992).

As reviewed by U.S. EPA (1985) and ATSDR (1989; 1991), trichloroethylene has been used as a surgical anesthetic, and effects on neurobehavior and the central nervous system are well studied in humans and animals exposed acutely to the inhaled compound. The effects of repeated exposures of humans to

trichloroethylene are less well studied. Occupational exposure to trichloroethylene in air has been associated with symptoms of effects on the central nervous system (e.g., nausea, headache, reduced cognitive performance, and sleep disturbances), but not on the kidney or liver (ATSDR, 1989, 1991; U.S. EPA, 1985; Nagaya et al., 1989; Ruijten et al., 1991). Data regarding effects in humans repeatedly exposed to trichloroethylene in drinking water are confounded by concurrent exposure to other chemicals (ATSDR, 1991; Goldberg et al., 1990). However, several studies are available in which animals have been repeatedly exposed to orally administered trichloroethylene. The data are reviewed herein, and a chronic RfD for trichloroethylene is derived.

CHRONIC ORAL TOXICITY

Nonneoplastic kidney lesions, in addition to carcinogenic responses, have been observed in studies designed to examine the carcinogenicity of chronic oral exposures to trichloroethylene in rodents.

NCI (1976) studied the carcinogenicity of trichloroethylene in corn oil in 78-week chronic gavage studies with rats and mice. The trichloroethylene sample used in these studies was $\geq 99.0\%$ pure, but contained 0.09% epichlorohydrin, a demonstrated carcinogenic agent.

Groups of 50 male and 50 female rats were provided time-weighted average doses of 549 or 1,097 mg/kg/day (NCI, 1976). A matched vehicle control group contained 20 males and 20 females, and an unmatched vehicle control group contained an additional 79 male rats and 78 female rats. Rats were allowed to survive until 32 weeks after exposure. The exposed rat groups did not display statistically significant increases in incidences of tumors compared with control rats, but both exposed groups displayed decreased peak body weights and survival compared with controls. Nephropathy was common in both treated groups. The nephropathy was described as slight to moderate degenerative and regenerative changes in the tubular epithelium; the authors stated that these lesions were unlike those that frequently occur in aging Osborne-Mendel control rats.

Groups of 50 male and 50 female B6C3F1 mice were provided time-weighted average doses of 1,169 or 2,339 mg/kg/day for males and 869 or 1,739 mg/kg/day for females (NCI, 1976). A matched vehicle control group contained 20 males and 20 females, and an unmatched control group contained an additional 57 male and 60 female mice. Significantly reduced survival was observed in both exposed groups compared with matched vehicle controls. Significantly increased incidences of liver tumors were observed in both exposed groups of both sexes compared with the matched vehicle control groups. The occurrence of nonneoplastic lesions of the kidney were not mentioned in the report of this study.

In a second series of chronic gavage studies, NTP (1988, 1990) studied the carcinogenicity of epichlorohydrin-free trichloroethylene in rats and mice. The test chemical (designated as "Hi-Tri") used in these studies was tested to be > 99.9% pure and contained 8 ppm diisopropylamine as a stabilizer.

Trichloroethylene in corn oil was administered by gavage at doses of 0 or 1000 mg/kg to groups of 50 male and 50 female B6C3F1 mice for 5 days/week for up to 103 weeks (NTP, 1990). Adjustment for partial weekly exposures gives average daily doses of 0 and 714 mg/kg/day. Statistically significant differences between dosed and control mice included decreased survival in males, decreased body weights in male mice, increased hepatocellular carcinoma incidence in both sexes, increased adenoma incidence in male mice, and toxic nephrosis in both sexes. Toxic nephrosis, described as cytomegaly of the renal tubular cells, was observed in 45/50 male and 48/49 female dosed mice, but was absent in the vehicle controls.

Groups of 50 male and 50 female F344/N rats were administered gavage doses of 0, 500 or 1000 mg/kg trichloroethylene in corn oil for 5 days/week for up to 103 weeks (average daily doses of 0, 357, and 714 mg/kg/day) (NTP, 1990). Statistically significant differences between dosed and control rats included decreased survival of both low- and high-dose male rats, decreased body weights in both sexes of rats at both doses, increased incidence of renal tubular adenocarcinomas in male rats killed at the end of the study, and cytomegaly of the kidney. Renal cytomegaly was observed in 96/98 dosed male and 97/97 dosed female rats; no vehicle control rats displayed renal cytomegaly.

In another bioassay, groups of 50 male and 50 female rats of four strains (ACI, August, Marshall, and Osborne-Mendel) were administered 0, 500 and 1000 mg/kg trichloroethylene in corn oil by gavage 5 days/week for 103 weeks (average daily doses were 0, 357 and 714 mg/kg/day) (NTP, 1988). Depressions in final body weights $\geq 10\%$, compared with controls, were observed in ACI, August and Osborne-Mendel male rats and Marshall female rats exposed to 1000 mg/kg; final body weight depression $\geq 10\%$ were observed only in ACI males at the 500-mg/kg dose level. Survival was significantly reduced in 7 of the 16 dosed groups compared with respective control groups. Clinical signs of central nervous toxicity (sedation, loss of consciousness, tremors, convulsions, and hindlimb paralysis) were observed following dose administration in male and female rats of all strains. Significantly increased incidence of renal tubular cell adenomas or adenomacarcinomas were observed only in low-dose male Osborne-Mendel rats, and interstitial cell neoplasms of the testis were observed in dosed Marshall rats. Exposure to trichloroethylene caused renal tubular cell cytomegaly in 82-100% of all dosed rats. Toxic nephropathy, described as dilated tubules lined by elongated and flattened epithelial cells, was observed in 17%-80% of the animals in the dosed groups. Cytomegaly or toxic nephropathy were not observed in untreated or vehicle control

groups. NTP (1988) concluded that these studies were inadequate tests of the carcinogenicity of trichloroethylene because of deficiencies in study-conduct and decreased survival, but clearly demonstrated the nephrotoxicity of trichloroethylene. NTP (1988) also concluded that the cause of early mortality in the dosed rats was not known but could have been due to gavage-related trauma, anesthetic properties of the chemical, nephrotoxicity or a combination of these factors.

SUBCHRONIC AND NEAR SUBCHRONIC ORAL TOXICITY

NTP has published results from 13-week gavage studies with rats exposed to trichloroethylene (NTP, 1988, 1990) and mice (NTP, 1990). The test chemical in this series of experiments was the same as designated for the chronic NTP studies reviewed in the previous section.

Groups of 10 male F344/N rats were administered gavage doses of 0, 125, 250, 500, 1,000 or 2,000 mg/kg trichloroethylene in corn oil 5 days per week for 13 weeks (NTP, 1990). Adjusting for the partial weekly exposure protocol, average daily doses are 0, 89, 179, 357, 714, or 1429 mg/kg/day. Groups of 10 female rats received doses of 0, 62.5, 125, 250, 500 or 1,000 mg/kg by the same schedule. (Adjusted doses were 0, 45, 89, 179, 357, or 714 mg/kg/day.) All rats survived to the end of the exposure period and only male rats dosed with 2,000 mg/kg exhibited depressions of body weight gain > 10%. Organ weight data were not reported. Histopathological examinations of major organs and tissues from the high-dose and control groups revealed cytomegaly and karyomegaly of the renal tubular epithelial cells in 8/9 high-dose males and 5/10 high-dose females, but not in the controls. The lesions were graded as minimal or mild in males and equivocal to minimal in females; these minimal renal effects were diagnosed during a reevaluation of the tissues after observation of pronounced renal effects in the subsequent 2-year study. Pulmonary vasculitis was observed in 6/10 high-dose males and 6/10 high-dose females (compared with 1/10 male and 1/10 female control rats).

In a separate rat study (NTP, 1988), groups of 10 male ACI and 10 male August rats were administered gavage doses of 0, 125, 250, 500, 1,000 or 2,000 mg/kg trichloroethylene in corn oil 5 days per week for 13 weeks (adjusted doses of 0, 89, 179, 357, 714, or 1429 mg/kg/day); groups of 10 females of these strains received doses of 0, 62.5, 125, 250, 500 or 1,000 mg/kg (adjusted doses of 0, 45, 89, 179, 357, or 714 mg/kg/day). Groups of 10 male Marshall rats received doses of 268, 308, 495, 932, or 1834 mg/kg by the same schedule (0, 191, 220, 354, 666, or 1310 mg/kg/day, adjusted doses); groups of 10 female Marshall rats received 0, 134, 153, 248, 466 or 918 mg/kg (0, 96, 109, 177, 333, 656 mg/kg/day, adjusted doses). All rats survived to the end of the study with the exception of 3 high-dose male August rats. Average depressions in final body weight > 10% (relative

to control values) were observed only in the high-dose male groups. Organ weight data were not reported. No clinical signs of central nervous system toxicity were recorded, and histological examination of major tissues and organs from high-dose rats did not reveal alterations compared with control tissues.

In the final NTP subchronic study (NTP, 1990), gavage doses of 0, 375, 750, 1500, 3000 or 6000 mg/kg were administered to groups of 10 male and 10 female B6C3F1 mice 5 days per week for 13 weeks (0, 268, 536, 1071, 2143, or 4286 mg/kg/day, adjusted doses). Deaths occurred in 2/10 males and 1/10 females at 1500 mg/kg, 7/10 males and 1/10 females at 3000 mg/kg, and all male and 9/10 females at 6000 mg/kg. Depressions in mean body weights were > 10% relative to controls in male mice receiving doses \geq 750 mg/kg; body weight alterations were not apparent in female mice. Liver weight elevations (both absolute and relative) > 10% relative to controls were observed in male mice at doses \geq 750 mg/kg and in females at doses \geq 1500 mg/kg. Centrilobular necrosis was observed in 6/10 males and 1/10 females exposed to 6000 mg/kg. At the 3000 mg/kg level centrilobular necrosis was not observed in either sex, but 2/10 males had multifocal areas of calcification in their livers. Histopathological examinations of tissues from mice treated with the 3 lowest doses were not conducted. Mild to moderate cytomegaly and karyomegaly of the renal tubular epithelial cells was observed in all of the mice that received the two highest doses and survived for more than 6 weeks.

Stott et al. (1982) administered gavage doses of trichloroethylene (> 99.9% pure, stabilized with diisopropylamine) in corn oil at levels of 0, 250, 500, 1200 or 2400 mg/kg, 5 days/week for 3 weeks to groups of 10-12 male B6C3F1 mice. Adjusting for the partial weekly exposures gives average daily doses of 0, 179, 357, 857, or 1714 mg/kg/day. No exposure-related effects were observed on body weight, kidney weight or kidney histopathology. Increased relative liver weights and decreased DNA content per gram of hepatic tissue were observed at doses \geq 500 mg/kg. Histopathological changes in hepatic tissues were observed at all dose levels. The severity of the changes increased with increasing dosage level. Slight increases in cytoplasmic eosinophilic staining of the centrilobular hepatocytes were observed at 250 and 500 mg/kg. At 1200 mg/kg increased centrilobular hepatocellular swelling was observed, and at 2400 mg/kg, more severe hepatocellular swelling, giant cell inflammation and mineralized cells were observed. Under the conditions of this study, the lowest dosage level of 250 mg/kg (179 mg/kg/day) was the LOAEL for response of the liver to trichloroethylene.

Stott et al. (1982) also administered gavage doses of trichloroethylene in corn oil of 0 or 1100 mg/kg, 5 days per week for 3 weeks, to groups of 4 male Osborne-Mendel rats. No treatment-related alterations in body weight, kidney weight,

histopathology of the kidney or liver, or DNA content per gram of renal or hepatic tissue were observed. Increased relative liver weight was the only significant treatment-related change observed in this study.

Tucker et al. (1982) provided trichloroethylene (reagent grade containing 0.004% diisopropylamine as stabilizer) in drinking water containing 1% emulphor at concentrations of 0, 0.1, 1.0, 2.5 and 5.0 mg/mL to groups of 30 male and 30 female CD-1 mice for 4 or 6 months. Average dosage levels estimated from water consumption data were reported to be 0, 18.4, 216.7, 393.0, and 660.2 mg/kg/day for males and 0, 17.9, 193.0, 437.1, and 793.3 mg/kg/day for females. No significant effects on weight gain were observed in the treated groups compared with the control group. The results of gross pathological examination of tissues at 4 and 6 months were reported to be unremarkable. Microscopic examinations of tissues and organs were not performed. Terminal body weights of male and female mice treated with the highest concentration of trichloroethylene were significantly decreased compared with the vehicle control terminal body weights. Increased relative liver weights were observed in males at both exposure times at the three higher doses and in females at the highest dose. Significantly increased kidney weights were observed in high-dose males at 4 and 6 months and in high-dose females at 6 months; urinalysis at 6 months of exposure showed elevated protein and ketone levels in high-dose females and males treated with the two highest concentrations of trichloroethylene. The NOEL of 0.1 mg/mL (18.4 mg/kg/day) and LOAEL of 1.0 mg/mL (216.7 mg/kg/day) for increased relative liver weight in mice describes the most sensitive toxicity threshold identified in this study. The LOAEL for kidney effects was 2.5 mg/mL (393 mg/kg/day).

In a study restricted to the hepatotoxicity of trichloroethylene, male Swiss-Cox mice (age 3-5 months, body weight 34-45 g) were administered distilled trichloroethylene (% purity not reported) in corn oil by gavage in doses of 0, 100, 200, 400, 800, 1600, 2400 or 3200 mg/kg on five days a week for 6 weeks (Buben and O'Flaherty, 1985). Adjusting for the partial weekly exposure gives average daily dosages of 71.4, 142.9, 285.7, 571.4, 1142.9, 1714.3 and 2285.7 mg/kg/day. Twelve mice per dosage were tested except for 5 mice at 100 mg/kg/day, 4 mice at 3200 mg/kg/day and 24 mice in the control group. The following endpoints were assessed on the day following treatment at all dosages: relative liver weight, liver glucose-6-phosphatase (G6P) activity, concentrations of liver triglycerides, serum glutamate-pyruvate transaminase (SGPT) activity. Liver DNA concentration and histology were evaluated at 285.7 and 1142.9 mg/kg/day. Statistically significant ($p < 0.05$) increases in relative liver weight at ≥ 71.4 mg/kg/day, G6P at ≥ 571.4 mg/kg/day, and SGPT at ≥ 1714.3 mg/kg/day were observed. The changes in relative liver weight and G6P were clearly dose-related. Liver triglycerides were significantly increased only at 1714.3 mg/kg/day ($p < 0.01$); a comparable

increase occurred at 2285.7 mg/kg/day but was not statistically significant, apparently due to the small number of animals (4). The increases in liver size were attributed to hepatocellular hypertrophy based on histology and decreased hepatic DNA concentrations. Other hepatic histologic effects included degeneration, karyorrhexis (disintegration of the nucleus) and polyploidy at 285.7 and 1142.9 mg/kg/day, and necrosis at 1142.9 mg/kg/day. The degeneration was manifested by swollen hepatocytes that were not due simply to edema, as liver wet weight/dry weight ratios did not increase. Under the conditions of this experiment, the lowest dosage level (71.4 mg/kg/day) was a LOAEL for a dose-related response of the mouse liver to trichloroethylene which caused hepatocellular hypertrophy, and progressing to hepatocellular necrosis.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In a 2-generation fertility study (NTP, 1986), groups of 20 F₀ breeding pairs of F344 rats (11 weeks of age at the start) were provided diets containing nominal trichloroethylene concentrations of 0.15, 0.30 and 0.60% for a 7-day mating period, a 98-day cohabitation period, and a subsequent 28-day segregation period. A control group of 40 F₀ breeding pairs was provided a normal diet for the same period of time. Trichloroethylene (designated as "Hi-Tri Purity grade") was microencapsulated in a gelatin/sorbitol shell. Estimated average dosage levels were calculated from initial and week 13 body weight data reported by the authors and the allometric equation recommended by the U.S. EPA (1987c) for calculating food consumption by laboratory mammals. The estimated doses for male F₀ rats were 0, 130.2, 261.1, and 523.9 mg/kg/day; for F₀ females the doses were 0, 147.8, 301.7, and 599.3 mg/kg/day.

Statistically significant ($p < 0.05$) differences between the dosed and control F₀ groups were not observed in the following parameters: the proportion of breeding pairs able to produce at least one litter, the number of live litters per pair, the number of live pups per litter, the proportion of pups born alive, the sex of pups born alive (NTP, 1986). Dam body weights on postnatal day 0 were significantly depressed in all of the exposed F₀ groups compared with the control. Statistically significant ($p < 0.05$) trends with increasing dose were observed for decreased numbers of live litters per pair and for decreased numbers of live pups per litter. A crossover mating trial was subsequently conducted using three combinations of F₀ breeding pairs (20 pairs per combination) as follows: control male x control female; 0.6% male x control female; and control male x 0.6% female. In this trial, the only significant differences between the mating pairs with exposed partners and the control pairs were decreased proportion of detected matings (observed when either the male or female partners were exposed), and decreased bodyweight of the 0.6% dams on postnatal day 0. Exposure of either the male or female partner had no significant

effect on the other indices of fertility and reproductive performance listed above for the initial F_0 breeding trial.

Continuous exposure of F_1 rats (81 days \pm 10) to the same dietary concentrations of trichloroethylene fed to their parents (14-20 breeding pairs were evaluated for each exposure level) had no effect on indices of mating, fertility or reproductive performance (NTP, 1986). As in the F_0 generation, treated F_1 dams displayed depressed body weight on postnatal day 0, indicating generalized maternal toxicity. Microscopic examination of major tissues and organs revealed no treatment-related pathological changes in either sex in the F_0 or the F_1 generations. At necropsy, body weights were depressed and liver weights (adjusted for body weight by an analysis of covariance) were increased in male and female F_0 rats treated with 0.6% trichloroethylene compared with control F_0 rats. F_1 male and female rats from all treatment groups displayed significantly decreased body weights at 21 and 81 (necropsy) days after birth. Significantly increased adjusted liver weights were observed for all treated F_1 male groups and for F_1 female rats treated with 0.3 or 0.6% trichloroethylene. Under the conditions of this experiment, the lowest exposure level (0.15% trichloroethylene) was a LOAEL for maternal toxicity demonstrated by decreased body weight (147.8 mg/kg/day), for decreased body weight and increased liver weight in F_1 males (130.2 mg/kg/day), and for decreased body weight in F_1 females (147.8 mg/kg/day).

In a similarly designed mouse study, NTP (1985) provided nominal concentrations of 0, 0.15, 0.30 and 0.60% trichloroethylene ("Hi-Tri Purity grade") in the diet of groups of breeding pairs of CD-1 mice starting at 11 weeks of age and continuing as described for the rat fertility study (NTP, 1986). The groups contained 35, 17, 18, and 19 pairs of mice, respectively. Average doses, in units of mg/kg/day, were reported to be 0, 63.8, 247.5, for week 1, 0, 52.5, 266.5, and 615.0 for week 2, and 0, 187.5, 375.0, and 750.0 for the remainder of the 18-week exposure period. Time-weighted average doses are calculated to be 0, 173, 362, and 737 mg/kg/day. No clinical signs of toxicity were observed throughout the exposure period. Indices of fertility and reproductive performance for the F_0 generation were not affected by exposure, except for a slight (< 10%), but statistically significant ($p < 0.05$), depression of birth body weights of live male pups or combined male and female pups compared with controls. The depression was only significant when adjustments were made for the total number of live and dead pups per litter by an analysis of variance.

Litters from the control and high-dose mouse groups were raised to sexual maturity to assess fertility and reproductive performance. Perinatal mortality was pronounced in the 0.6% group; a 61.3% mortality rate was observed compared with a 28.3% mortality rate for the control group. Survival after weaning was the same for both control and exposed F_1 groups. Surviving F_1 mice were provided the same feed level of trichloroethylene as

their parents for 74 ± 10 days; breeding pairs were then established and the F_1 females were allowed to deliver their litters. Indices of mating, fertility or reproductive performance for the 0.6% F_1 group were not significantly different from those for the control group.

Tissues from the control and high-dose F_0 and F_1 mice were weighed and examined microscopically (approximately 18 and 15 weeks of exposure for the F_0 and F_1 generations, respectively). Body weights at necropsy were not affected by high-dose exposure in either generation. Liver weights (absolute and adjusted) were increased by high-dose exposure in both sexes of both generations. Liver and kidney lesions (hypertrophy of the centrilobular liver cells and tubular degeneration and karyomegaly of the renal tubular epithelium) were also observed in high-dose F_0 and F_1 mice of both sexes. Significantly decreased proportions of sperm that were motile were observed in high-dose F_0 and F_1 males (45 and 18% decreases compared with controls). In summary, although trichloroethylene treatment at dietary concentrations as high as 0.6% did not alter several indices of fertility or reproductive performance, organ-specific effects on the F_0 and F_1 male reproductive tract and increased perinatal mortality of F_1 pups were observed. The authors concluded that trichloroethylene may present a selective risk to the neonatal mouse (NTP, 1985). The study identified 0.6% (737 mg/kg/day) as a FEL for the effects on the male mouse reproductive tract and neonatal survival, but did not identify a NOEL or NOAEL for these effects (neither endpoints were assessed at the lower exposure levels).

Manson et al. (1984) administered gavage doses of 0, 10, 100 or 1000 mg/kg trichloroethylene in corn oil to groups of 23 female Long-Evans hooded rats. Exposure commenced 2 weeks before mating, continued throughout mating (1 week), and was stopped on day 21 of pregnancy. Doses were administered 5 days/week for the first 3 weeks and 7 days/weeks for the last 3 weeks. Adjusting for the partial weekly exposure during the first part of the study, average daily doses were 0, 8.6, 85.7, or 857.1 mg/kg/day. Females were bred to untreated males. Indices of fertility (i.e., the average number of mating trials required for insemination and the number of rats which became pregnant) were not affected by exposure to any level of trichloroethylene. Maternal body weight gain during pregnancy, litter size at birth, and neonatal survival (up to 31 days after birth) were not altered in the groups exposed to 10 or 100 mg/kg. Body weight gains during the premating period and during pregnancy were significantly depressed only in the high-dose dams, as was decreased neonatal survival up to 18 days after birth (16.9% of 1000-mg/kg pups died compared with 7.7% in the control). Four deaths occurred among the 23 dams exposed to 1000 mg/kg. No major malformations were revealed by gross examinations of the pups. The authors speculated that the decreased neonatal survival was related to maternal toxicity rather than to specific

developmental toxicity. Under the conditions of this study, 100 mg/kg (85.7 mg/kg/day) was the NOAEL, and 1000 mg/kg/day (857.1 mg/kg/day) was the LOAEL for maternal toxicity and FEL for decreased neonatal survival.

DERIVATION OF A PROVISIONAL RfD

The chronic and subchronic mouse and rat gavage bioassays conducted by NCI (1976) and NTP (1988, 1990) identify the kidney (in mice and rats) and the liver (in mice) as target organs for trichloroethylene-induced nonneoplastic effects, however the data are not suitable bases for an RfD. The lowest doses in the chronic studies produced reduced survival, and, as FELs, cannot be used to derive an RfD. Deficiencies in the design of the subchronic NTP (1988, 1990) studies compromise their usefulness; histological examinations were conducted only on high-dose animals and controls, and organ weight data was reported for only one of the studies. In general, the NTP studies provide insufficient information for exposure to doses less than 500 mg/kg, a level identified as producing frank effects; the only exception is the mouse subchronic study (NTP) which identified 375 mg/kg (268 mg/kg/day adjusted for partial weekly exposure) as a NOAEL and 675 mg/kg as the LOAEL for increased liver weight in male mice. Other subchronic studies are available that identified LOAELs lower than 268 mg/kg/day (NTP, 1986; Tucker et al., 1982; Buben and O'Flaherty, 1985) .

The 2-generation fertility study of B6C3F1 mice (NTP, 1985) indicated that reduced neonatal survival during lactation is a significant effect produced by exposure to trichloroethylene. However, the study did not identify a NOAEL for this frank effect, and thus the data cannot be used to derive an RfD.

The 2-generation fertility study of F344 rats exposed to trichloroethylene in the diet (NTP, 1986) identified a free-standing LOAEL of 130.2 mg/kg/day for decreased body weight and increased liver weight in F₁ male rats exposed for 18 weeks to trichloroethylene; indices of fertility and reproductive performance and histological features of major organs and tissues in rats exposed to this dose or higher doses were not significantly different from comparable endpoints in controls.

While the 1986 NTP study is suitable for consideration as a basis for the RfD, the 6-month drinking water study of mice by Tucker et al. (1982) provides a better basis because it identified both NOAELs and LOAELs for the responses of the liver and kidney to orally administered trichloroethylene. The threshold for liver toxicity (NOAEL of 18.4 and LOAEL of 216.7 mg/kg/day for increased relative liver weight) was lower than that for renal effects (NOAEL of 216.7 and LOAEL of 393.0 mg/kg/day for elevated levels of protein and ketones; increased kidney weight was observed at the highest dose, 660.2 mg/kg/day).

Although the Tucker et al. (1982) study did not include histological examinations of the liver and kidney, a more comprehensive examination of hepatotoxicity in mice orally exposed to trichloroethylene for 6 weeks showed that liver weight increases were attributable to hypertrophy of the liver cells and that the hepatic response progressed to degenerative changes at higher doses (Buben and O'Flaherty, 1985). The study by Tucker et al. (1982) is a better basis for derivation of the RfD than the study by Buben and O'Flaherty (1985) because a NOAEL was identified and the duration of exposure was closer to a life-time.

A provisional chronic RfD of $6E-3$ mg/kg/day is derived by dividing the mouse NOAEL of 18.4 mg/kg/day from the study by Tucker et al. (1982) by an uncertainty factor of 3000 (10 for interspecies extrapolation, 10 for intraspecies variation, 10 for extrapolation to chronic duration and 3 for weakness of the data base).

Confidence in the principal study is low. Adequate numbers of animals were exposed by a relevant route and were evaluated for several endpoints. However, histological examinations were not conducted on the tissues, and the duration of exposure was only one-quarter of a life-time. Confidence in the data base is low. Several subchronic toxicity studies in rats and mice are available, as are studies of reproductive performance in rats and mice. However, chronic oral bioassays do not adequately describe dose-response relationships for chronic oral exposure to low doses of trichloroethylene and comprehensive developmental toxicity studies are not available. Reflecting low confidence in the principal study and the data base, confidence in the provisional RfD for trichloroethylene is low.

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